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(12) # EUROPEAN PATENT APPLICATION

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(54) **Pharmaceutical compositions.**

(57) A pharmaceutical composition comprising γ-linolenic acid and/or dihomo-γ-linolenic acid and a conjoint amount of thioproline or other administrable reverse transformer, for treatment of cancer.

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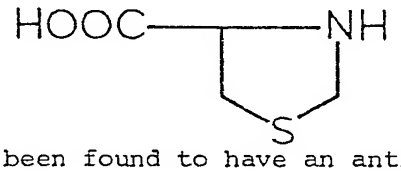
"PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

This invention relates to the treatment of cancer primarily, but not exclusively, in the field of human medicine, and to compositions for use therein.

TRANSFORMATION

The drug thioproline (thiazolidine-4-carboxylic acid), of formula 

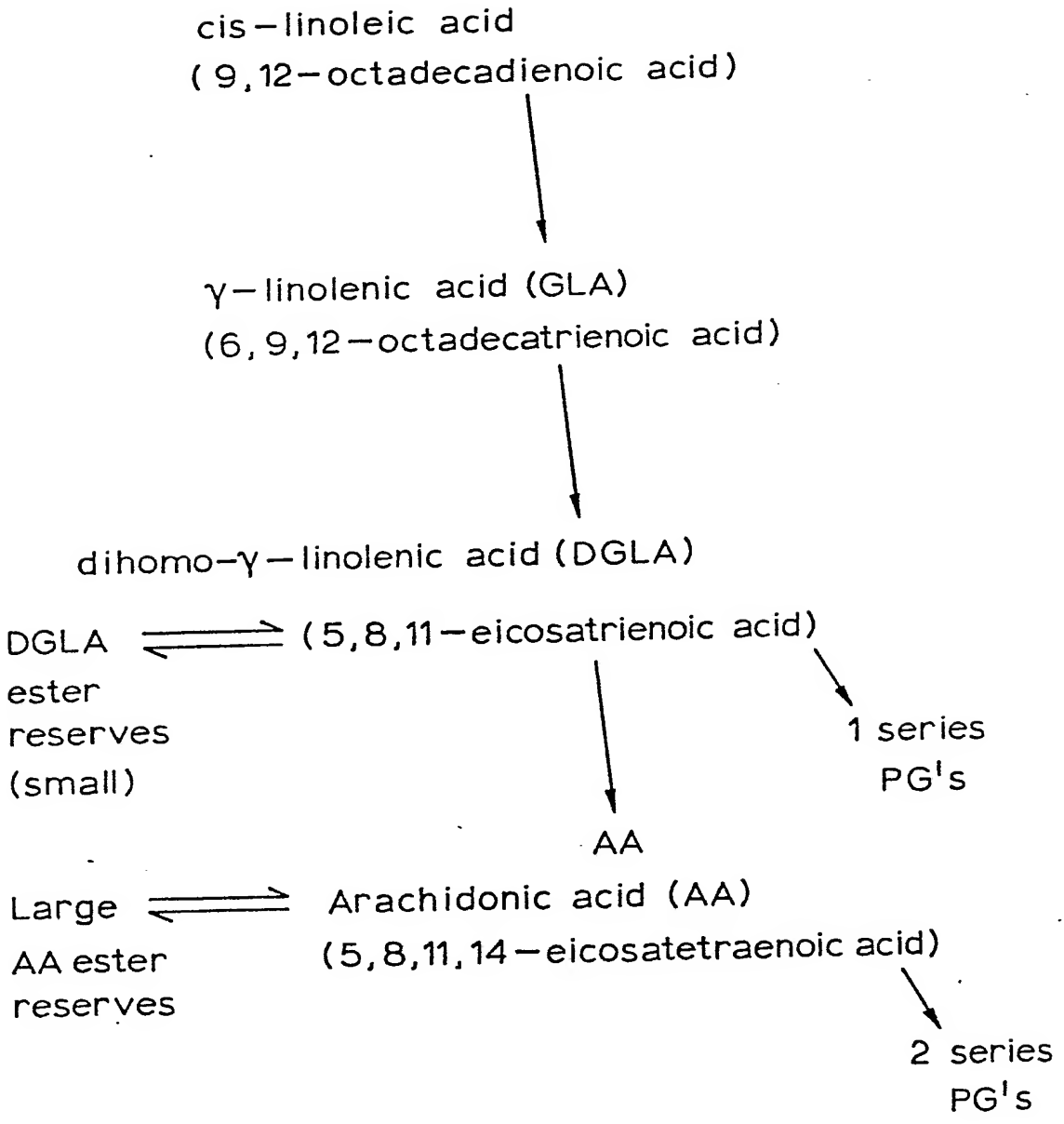
has recently been found to have an anti-cancer effect in humans (Brugarolas et al. Lancet, page 68, 12th January 1980). The effect of the drug was discovered because of its ability to induce what is known as reverse transformation in certain cultured cell lines.

These cell lines, derived from normal human and animal cells, behave in many respects like spontaneously occurring cancer cells. Normal cells can be transformed by agents such as radiation, infection with certain viruses and by chemical carcinogens. The transformed cells multiply rapidly, like cancer cells, and generally show the morphological and biochemical characteristics of such cells, as discussed further for example in Johnson et al, Proc. Nat. Acad. Sc. U.S.A., 68 425-429 (1975) and Puck, ibid, 74 4491-4495 (1977).

RELATION TO ESSENTIAL FATTY ACID METABOLISM

One particular characteristic shown by human and animal cancer cells and by transformed cells is a consistent absence of the enzyme delta-6-desaturase which converts linoleic acid to γ-linolenic acid. The inventor believes that this fact is of great significance and that faulty essential fatty acid metabolism is a key factor in cancer.

The pathways of EFA transformation in the body are in outline as below:


cis-linoleic acid
(9,12-octadecadienoic acid)
γ-linolenic acid (GLA)
(6,9,12-octadecatrienoic acid)
dihomo-γ-linolenic acid (DGLA)
DGLA ester reserves (small)
(5,8,11-eicosatrienoic acid)
1 series PG's
AA
Large AA ester reserves
Arachidonic acid (AA)
(5,8,11,14-eicosatetraenoic acid)
2 series PG's

The broad outline of the pathways is well known, and it brings out clearly that a major function of essential fatty acids (EFAs) is to act as precursors for prostaglandins, 1-series PGs being formed from dihomo-γ-linolenic acid (DGLA) and 2-series PGs from arachidonic acid (AA). DGLA and AA are present in food in only small quantities, and the major EFA in food is linoleic acid which is first converted to γ-linolenic acid (GLA) and then to DGLA and AA. The conversion of linoleic acid to GLA is blocked by a high fat and high carbohydrate diet, by ageing and for example by diabetes. Stores of AA in the body in the form of lipid esters are very large indeed. In contrast only small amounts of DGLA ester are present.

DGLA is the key substance. GLA is almost completely and very rapidly converted in the body to DGLA and so for practical purposes the oral administration of DGLA and GLA amount to the same thing. DGLA can be converted to a storage form, or to PGs of the 1-series, or to arachidonic acid and thence to PGs of the 2-series. The conversion to arachidonic acid is irreversible.

Accordingly it can be seen that since γ-linolenic acid is a necessary precursor of dihomo-γ-linolenic acid and thus of 1-series PGs, and since also cellular stores of DGLA are very limited, cancer cells and transformed cells soon lose the ability to make 1-series PGs and in particular the important compound PGE 1.

SIGNIFICANCE

The inventor believes that many of the characteristic features of transformed and cancer cells are due to this damage to PG metabolism and accordingly further that thioproline and other inducers of reverse transformation will be more effective in the treatment of cancer, particularly in the long term, if they are supported by measures to restore production of 1-series PGs and particularly PGE 1 in the cells. Such measures lie in particular in the provision of GLA or DGLA from either natural or synthetic sources,

to by-pass the block at the delta-6-desaturase and enable cells which had lost the enzyme to continue to make PGE 1.

It may be noted that having regard to the inventor's view of the connection between 1-series PG metabolism and reverse transformation, it would be expected that substances such as PGE 1 might themselves induce the reverse transformation process. It is therefore significant that it is in fact known that PGE 1 is able to induce reverse transformation in cultured cells, possibly through stimulating production of a nucleotide known as cyclic AMP which is also known to induce the transformation. These reverse transformation inducing properties have been known since 1971, but the inventor believes that he is the first to recognise their significance in the present context through his concern with prostaglandin metabolism generally, shown for example in his previous patent applications referred to below. Through his approach, it has been possible to see that, while substances such as PGE 1 and cyclic AMP would never be thought of as possible components of therapeutic compositions, being unstable and generally unsuitable for adminstration, restoration of the natural in situ production of 1-series PGs and in particular PGE 1 is of great value. This value has been shown directly in the female Fisher rat where the growth in both size and weight of the transplantable R3230AC mammary tumour is halved by 25 µl Evening Primrose oil daily, as a GLA source directly favouring 1-series PG production. Moreover direct evidence of effectiveness of administration of GLA in the form of Oenothera seed oil, combined with Vitamin C, has already been obtained from early results in a group of cancer patients in a Scottish hospital. One man with a papillary bladder carcinoma of fifteen years standing and beyond help by surgery, radiotherapy or conventional chemotherapy has had haematuria controlled over more than a year, with accompanying well being rather than the well known toxic effects of conventional treatments.

Similarly, a woman with the whole abdomen infiltrated with an anaplastic carcinoma extensively palpable and confirmed by histological examination, untreatable by normal means, has shown complete regression of the tumours to palpation over a period of fifteen months, again with accompanying well being. Such results indicate the value of the combined approach of such measures with the present invention discussed below.

THE INVENTION

The invention accordingly lies in the use of thioproline particularly and, more generally, agents suitable for therapeutic administration and capable of bringing about reverse transformation, in combination with γ-linolenic acid and/or dihomo-γ-linolenic acid, optionally in association with linoleic and if desired other fat acids, said thioproline or other reverse transformer and/or γ-linolenic or dihomo-γ-linolenic acids being used if desired as physiologically functional salt, ester or other derivatives thereof. Both the compositions of these materials and their use administered separately or together in the treatment of cancer are within the purview of the invention.

RELATIONSHIP TO PREVIOUS PROPOSALS

The above approach may be used in combination with the use of other materials as disclosed in the inventor's pending European Patent Applications Nos. 79.300079.5, 79.300546.3 and 80.301510.6 (Publication Nos.0003407, 0004770 and 0019423) and U.S. Patent Application Nos. 004 924, 029 058 and 150 402.

These materials include zinc, penicillin and β-lactam antibiotics generally,(European Patent Application No. 79.300079.5 etc) and also penicillamine, phenformin and levamisole (European Patent Application No. 79.300546.3 etc) when the other effects of these materials are acceptable, all of which are believed to enhance mobilisation of DGLA reserves and hence ensure that administered GLA and DGLA go into synthesis of PGs. The materials

also include ascorbic acid, ethyl alcohol, and naloxone, nalorphine, levallorphan and other opiate antagonists (European Patent Application No. 80.301510.6 etc.), a class which enhance physiological synthesis of 1-series PGs from DGLA without substantially enhancing synthesis of 2-series PGs from AA.

Further, there is evidence that thromboxane A2 (produced in the body along with the endoperoxides giving rise to 2-series PGs) indirectly enhances formation of PGE 1. Substances such as colchicine, amantadine, griseofulvin; vinblastine, vincristine and other Vinca alkaloids; interferon and melatonin, which are also discussed in the pending patent applications (European Patent Application No. 79300546.3 etc) and which seem to increase production or action of thromboxane A2, are thus also desirably used in the compositions of the present invention.

Reference may be made to the above published specifications for further details. The materials of the present invention may also be used in conjunction with the materials disclosed in unpublished pending Application No.
namely chloroquine and other 4-aminoquinolines including amodiaquine and hydroxychloroquine; diidohydroxyquin and other 8-hydroxy and 8-aminoquinolines including iodochlorhydroxyquin, chiniofon, pentaquine, isopentaquine and primaquine; quinacrine (mepacrine) and other acridines; quinidine, quinine and procaine; emetine, metronidazole and other antiprotozoals (not already named above); and spironolactone and other modified steroids, all of which influence the 1-series/2-series PG balance in the body in favour of 1-series PGs.

The purpose of these materials is thus not only to help in the restoration of 1-series PG production but to maintain a proper 1-series/2-series PG balance.

EFFECTIVE AGENTS

Thus DGLA or GLA from any natural or synthetic source alone

or with one or more of the agents discussed above is proposed for use with reverse transformation inducing agents to restore 1-series PG production.

Convenient physiologically functional derivatives of γ-linolenic acid and dihomo-γ-linolenic acid for use according to the invention include the C_1-C_4 alkyl (e.g. methyl and ethyl) esters and the glycerides of the acids.

If desired, pharmaceutical compositions may be produced for use in the invention by associating natural or synthetic γ-linolenic acid (or a physiologically functional derivative thereof) and/or dihomo-γ-linolenic acid (or a physiologically functional derivative thereof), as such, with an acceptable pharmaceutical vehicle. It is at present convenient to incorporate the γ-linolenic acid into compositions in the form of an available oil having a high γ-linolenic acid content, hence references to "oil" herein.

At the present time known natural sources of oils having a high γ-linolenic acid content are few (there are no known natural sources of significant amounts of dihomo-γ-linolenic acid). One source of oils currently available is the seed of Evening Primrose species such as Oenothera biennis L. and Oenothera lamarckiana, the oil extract therefrom containing γ-linolenic acid (about 8%) and linoleic acid (about 72%) in the form of their glycerides together with other glycerides (percentages based on total fatty acids). Another source of γ-linolenic acid is Borage species such as Borago officinalis which, though its current yield per acre is low, provides a richer source of γ-linolenic acid than Oenothera oil. Recent studies on fungi which can be cultivated by fermentation promise a fungal oil source.

The seed oil extracts referred to above can be used as such or can for example if desired be fractionated to yield an oily composition containing the triglycerides of γ-linolenic and linoleic as the main fatty acid components, the γ-linolenic acid content

being if desired a major proportion. Seed oil extracts appear to have a stabilising effect upon any dihomo-γ-linolenic acid or physiologically functional derivative thereof incorporated therein.

AMOUNTS OF γ-LINOLENIC ACID AND RELATED MATERIALS

A preferred daily dosage for all purposes for an adult (weight ca 75 kg) is from 0.05 to 0.1 up to 1, 2, 5 or even 10 g as required of γ-linolenic acid or equivalent weight (calculated as γ-linolenic acid) or a physiologically functional derivative thereof. Amounts may in particular be 0.1 to 1.0 g daily. Such doses correspond to about 2 to 20 g daily of the Oenothera oil discussed below. In place of, or in addition to, γ-linolenic acid, one may use dihomo-γ-linolenic acid or a physiologically functional derivative thereof in amount equivalent in molar terms to γ-linolenic acid and calculated as such. This dosage can for example be taken as a single dose or divided into 2, 3 or 4 subdivisions thereof as convenient.

AMOUNT OF THIOPROLINE

Amounts may be for example 100 mg to 35 g/day, conveniently 40 mg/kilo body weight/day (ca 3 g/day).

AMOUNTS OF OTHER ACTIVE MATERIALS

Amounts of materials used as referred to above to augment the effect of the GLA and/or DGLA may for example be:

I	Zinc	2.5 to 800 mg/day, preferably 10-80 mg, calculated as zinc
	Penicillin V or other β-lactam antibiotics	0.5 to 10 g/day
	Penicillamine	50 mg to 10 g/day
	Phenformin	10 mg to 5 g/day
	Levamisole	10 mg to 2 g/day
II	Colchicine	0.3 to 15 mg/day, preferably 0.6 to 2.4 mg
	Amantadine	100 to 1000 mg/day
	Griseofulvin	0.5 to 5 g/day
	Vinblastine	35 to 350 mg/week
	Vincristine	7 to 70 mg/week
	Interferon	1×10^5 to 1×10^8 units /day
	Melatonin	10 mg to 5 g/day
III	Ascorbic acid	50 mg to 50 g/day
	Ethyl alcohol	5 to 500 ml/day
	Naloxone	0.1 to 500 mg/day
	Nalorphine	1 mg to 5 g/day
	Levallorphan	0.2 mg to 1 g/day
	or like amounts of other opiate antagonists	
IV	Chloroquine and other materials listed with it earlier, as follows:	
	Quinoline derivatives	250 mg/week to 2500 mg/day
	Acridine derivatives	100 to 2500 mg/day
	Quinine	100 mg to 10 g/day
	Quinidine	100 mg to 2 g/day
	Procaine	100 mg to 10 g/day
	Spironolactone or other steroid derivatives	30 mg to 2 g/day
	Emetine	10 to 100 mg/day
	Metronidazole	100 mg to 10 g/day

PACKS

If it is not desired to have compositions comprising active materials listed above, packs may be prepared comprising the materials presented for separate or part joint and part separate administration in the appropriate relative amounts, and such packs are within the purview of the invention.

DIETARY COMPOSITIONS

The invention is chiefly described in terms of pharmaceutical compositions, but it will be understood that the γ-linolenic and other acids, being in the nature of dietary supplements, could be incorporated in a dietary margarine or other foodstuffs; such foodstuffs, possibly containing other active materials and generally referred to in this description as dietary or pharmaceutical compositions, are within the purview of the invention and thus of the term pharmaceutical compositions, packs or the like used herein.

VETERINARY APPLICATIONS

It will be understood that where a disorder of a kind calling for treatment in animals arises, the invention while described primarily in terms of human medicine and treatment is equally applicable in the veterinary field.

PHARMACEUTICAL PRESENTATION

The compositions according to the invention are conveniently in a form suitable for oral, rectal, parenteral or topical administration in a suitable pharmaceutical vehicle, as discussed in detail for example in U.K. Patent Specification No. 1 082 624 and in any case very well known generally for any particular kind of preparation. Thus for example tablets, capsules, ingestible liquid or powder preparations, creams and lotions for topical application, or suppositories, can be prepared as required. Injectable solutions of hydrolysed Oenothera oil may be prepared using albumin to solubilise the free acid.

Advantageously a preservative is incorporated into the preparations. α-Tocopheral in a concentration of about 0.1% by weight has been found suitable for the purpose.

It will be understood that the absolute quantity of active ingredients present in any dosage unit should not exceed that appropriate to the rate and manner of administration to be employed

but on the other hand should also desirably be adequate to allow the desired rate of administration to be achieved by a small number of doses. The rate of administration will moreover depend on the precise pharmacological action desired.

The following Examples serve to illustrate pharmaceutical compositions useful in treatment according to the invention:

EXAMPLES

Pharmaceutical compositions containing a unit dose of an oil extract from the seeds of Oenothera biennis L. optionally with methyl dihomo-γ-linolenate and/or zinc oleate, penicillin V, colchicine or any of the other active materials referred to herein, are prepared by encapsulation of the natural oil in soft gelatin capsules manufactured by known methods.

The oil is extracted from the seeds by one of the conventional methods of extraction such as cold pressure, screw pressure after partially cooking the seed, or solvent extraction.

Fractionation of a typical sample of this oil shows a yield of 97.0% oil in the form of methyl esters, with the relative proportions:

Palmitate	6.15
Steerate	1.6
Oleate	10.15
Linoleate	72.6
γ-linolenate	8.9

As preservative, α-tocopherol is added to the oil in a concentration of 0.1%.

Gelatin capsules containing oil extracts prepared as described above, each having the following contents of active ingredients (0.5 g oil extract = ca 0.045 g γ-linolenic acid), are prepared in conventional fashion.

EXAMPLE 1

The following capsules may be given, two capsules three

times a day, in the treatment of cancer:

Capsules containing:

Oil extract	0.5 g
Thioproline	500 mg

FURTHER EXAMPLES A

Similarly capsules containing additional materials may be administered, for example, 10 mg methyl dihomo-γ-linolenate per capsule as a direct supplement to the oil; or for example for their indirect action zinc oleate 10 mg or penicillin V 0.25 g (compare the Examples of European Patent Application No. 79300079.5 or U.S. Patent Application No. 004 924 referred to earlier); or phenformin 25 mg, levamisole 25 mg or penicillamine 100 mg per capsule, or colchicine 0.2 mg, amantadine 100 mg or griseofulvin 0.5 mg per capsule (compare the Examples of European Patent Application No. 79300546.3 or U.S. Patent Application No. 029 058 referred to earlier and also the use in conjunction with vincristine, vinblastine, melatonin and interferon referred to therein); or ascorbic acid 100 mg, naloxone 5 mg, nalorphine 5 mg or levallorphan 5 mg (compare the Examples of European Patent Application No. 80301510.6 or U.S. Patent Application No. 150 402 referred to earlier and also the use in conjuction with ethyl alcohol to give 30 to 300 mg% alcohol in the body referred to therein).

FURTHER EXAMPLES B

Other materials that may be incorporated in capsules as in Example 1 are for example chloroquine 50 mg, spironolactone 50 mg, quinacrine 50 mg, quinine or quinidine 50 mg, emetine 50 mg, or procaine 100 mg. These materials are among those which our unpublished co-pending application, referred to earlier, discloses.

It will be understood throughout that while a full theoretical discussion of what is believed to be the reason for the effectiveness of the compositions proposed is given to aid understanding, the invention is in no way to be limited by this discussion.

CLAIMS

1. A pharmaceutical composition comprising γ-linolenic acid or physiologically functional derivative thereof and/or dihomo-γ-linolenic acid or physiologically functional derivative thereof and a conjoint amount of thioproline or other administrable reverse transformer, alone or in an acceptable pharmaceutical vehicle.

2. A composition according to claim 1 comprising further a material influencing the 1-series/2-series PG balance in the body in favour of 1-series PG's.

3. A composition according to claim 2, wherein said material influencing the PG balance is selected from physiologically assimilable zine, a β-lactam antibiotic, penicillamine, phenformine or levamisole.

4. A composition according to claim 2, wherein said material influencing the PG balance is selected from colchicine; vinblastine, vincristine and other Vinca alkaloids; griseofulvin; amantadine; melatonin; and interferon.

5. A composition according to claim 2, wherein said material influencing the PG balance is selected from Vitamin C; ethyl alcohol; and naloxone, nalorphine, levallorphan and other opiate antagonists.

6. A composition according to claim 2, wherein said material influencing the PG balance is selected from chloroquine and other 4-aminoquinolines including amodiaquine and hydroxychloroquine; diidohydroxyquin and other 8-hydroxy and 8-aminoquinolines including iodochlorhydroxyquin, chiniofon, pentaquine, isopentaquine and primaquine; quinacrine (mepacrine) and other acridines; quinidine, quinine and procaine; emetine, metronidazole and other antiprotozoals (not already named above); and spironolactone and other modified steroids.

7. A composition according to claim 1, presented for administration in quantities to give 0.05 to 10g/day of said γ-linolenic or dihomo-γ-linolenic acid or derivative, calculated as γ-linolenic acid

8. A composition according to claim 1, presented for administration in quantities to give 100 mg to 35g/day thioproline.

9. A composition according to claim 3, presented for administration in quantities to give 2.5 to 800 mg/day zinc, 0.05 to 10g/day β-lactam antibiotic, 50 mg to 10g/day penicillamine, 10 mg to 5g/day phenformin or 10 mg to 2g/day levamisole.

10. A composition according to claim 4, presented for administration in quantities to give doses of:

0.3 to 15 mg/day colchicine
100 to 1000 mg/day amantadine
0.5 to 5 g/day griseofulvin
35 to 350 mg/week vinblastine
7 to 70 mg/week vincristine
1×10^5 to 1×10^8 units/day interferon, or
10 mg to 5 g/day melatonin.

11. A composition according to claim 5, presented for administration in quantities to give doses of:

50 mg to 50 g/day ascorbic acid or
5 to 500 ml day ethyl alcohol or
0.1 to 500 mg/day naloxone, 1 mg to 5 g/day nalorphine, 0.2 mg to 1 g/day levallorphan or like amount of other opiate antagonist

12. A composition according to claim 6, presented for administration in quantities to give doses of 250 mg/week to 2500 mg/day of the quinoline derivative; 100 to 2500 mg/day of said acridine derivative; 100 mg to 10 g/day of quinine, 100 mg to 2 g/day of quinidine, or 100 mg to 10 g/day of procaine; 30 mg to 2 g/day of said steroid; or 10 to 100 mg/day emetine; or 100 mg to 10 g/day metronidazole.

13. A composition according to any preceding claim, wherein the γ-linolenic acid is present in the form of the oil of the seed of Oenothera biennis, O. lamarckiana or other Evening Primrose species, or a fraction thereof.

14. A composition according to any preceding claim, wherein the γ-linolenic acid is present in the form of the oil of the seed of Borago officinalis or other Borage species, or a fraction thereof.

15. A composition according to any preceding claim, for use in treatment of cancer.

16. A pharmaceutical pack comprising the materials set out in any preceding claim presented separately, or one or more separately and others together, but for conjoint administration.

17. A method of treating cancer, comprising administering conjointly to a sufferer therefrom effective amounts of the materials specified in any preceding claim, separately or together.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number: EP 81 30 0867

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D	EP - A - 0 003 407 (VERRONMAY LTD.) * Page 18, line 1 - page 20, line 5, claims 1-20 *	1-16
D	EP - A - 0 004 770 (VERRONMAY LTD.) * Page 23, line 1 - page 25, line 14, claims 1-20 *	1-16
	US - A - 3 993 775 (JOHN WILLIAMS) * Column 2, lines 21-40; column 8, lines 15-21, claim 1 *	1-16
	BE - A - 867 787 (KALI-CHEMIE PHARMA GmbH) * Page 10, lines 1-4, lines 16-26, lines 32-38; claims 1,5,6,7,9 *	1-16
	FR - M - 3 184M (SOGESPAR S.A.) * Page 7, column 2, abstract *	1

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CLASSIFICATION OF THE APPLICATION (Int Cl.³)

A 61 K 31/425
A 61 K 31/43
31/44
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31/585
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45/02
45/06

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

A 61 K 31/425
31/43
31/47
31/49
31/585
31/475
31/485
33/30
45/02
C 07 D 277/06

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely:

Claims not searched: 17

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See Art. 52(4) of the European Patent Convention)

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
The Hague	02-07-1981	BRINKMANN

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application number EP 81 30 0867

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	FR - M - 1 592M (ASCHAFFENBURGER ZELLSTOFFWERKE A.G.) * Page 2, column 2,(eaux capillaires), page 4, column 2, abstract * --	1	
ED	EP - A - 0 019 423 (EFAMOL LTD.) * Pages 25-26, claims 1-10 * --	1	
P	FR - A - 2 444 459 (GOSALVEZ GOSALVEZ) * Page 13, lines 7-10, 27-29; claims 11,17 * & GB - A - 2 039 736 ----	1-16	TECHNICAL FIELDS SEARCHED (Int. Cl.³)